REMARKS

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, Claims 66-68, and 73-89 are pending. Claims 66, 81 and 85 have been amended. No new matter is introduced and the entry is respectfully requested. In the Office Action of October 6, 2003, the Examiner set forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

Rejections Under 35 U.S.C. § 102

In the Office Action of August 12, 2004, Claims 66-68 and 73-75, 81-82 and 87-89 stand rejected under 35 U.S.C. § 102 as being purportedly anticipated by Ishizaka et al., U.S. Patent No. 5,786,168 (the '168 patent) for the reasons set forth on page 3 of the Outstanding Office Action and for the reasons set on page 2 of the Office Action of October 12, 2004. Although Applicant argued that GIF and MIF are biologically distinct proteins, the Examiner maintained that "all that is necessary is an antibody which specifically binds SEQ ID NO:5. Since the prior art teaches an antibody which specifically binds the claimed SEQ ID NO:5, the claim is anticipated." Independent Claims 66, 81 and 85 have been amended. Accordingly, the Examiner's contention is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. Verdegaal Bros. v. Union Oil Co. Of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of

ordinary skill in the field of the invention. Scripps Clinic Research & Foundation v. Genentech Inc., 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

In this case, the present Claim 66 is directed to a **diagnostic** method **for determining** the amount of macrophage migration inhibitory factor **(MIF)** in a sample using an **anti-MIF antibody** which binds **specifically** to the human MIF protein that has a **molecular weight of approximately 12.5 kDa** and has **MIF biological activity**.

In contrast, the '168 patent generally describes a method for producing a substantially pure biologically active antigen non-specific GIF. The '168 patent does not disclose a diagnostic method for determining the amount of MIF has a molecular weight of approximately 12.5 kDa and has MIF biological activity. Furthermore, the '168 patent provides no evidence that the anti-GIF mAb(s) specifically recognize MIF. There is no proof in the patent itself, or in the relevant publications, that the anti-GIF mAb is actually MIF-specific. The anti-GIF mAb may cross react with MIF or other proteins. However, for the purpose of conducting a **diagnostic** test to detect MIF, the antibody must be MIF-specific. In particular, Applicant would like to call the Examiner's attention to the following facts in the '168 patent:

1. Ishizaka et al. specifically disclose in the '168 patent that the recombinant GIF produced in *E. coli* failed to inhibit the migration of human monocytes, and "[t]he results indicated that rhGIF was different from MIF in biological activity." (col. 46, line 47 to col. 47, line 4). In contrast, the present Claim 66 recites a protein having MIF activity.

2. GIF is cited in the literature as having a molecular weight of 14.4 kDa, which is almost 2000 daltons larger than MIF. The instant Claim 66 recites a 12.5 kDa MIF molecule. Further, MIF forms multimers, giving rise to additional species of approximately 25 kDa (dimer) and 37 kDa (trimer). Neither of these additional species of molecule is observed in the blots using anti-GIF antibody.

3. The anti-lipomodulin-enriched (not purified) GIF preparations in the '168 patent were used to immunize rats to generate mAbs. Several mAbs were generated that reacted with GIF, defined as species of 14.4 kDa and >41 kDa, neither of which is consistent with the MIF monomer or multimers of ~12.5 kDa.

4. GIF was enriched (not purified) with an anti-lipomodulin antibody (141-B9). That an anti-lipomodulin antibody can be used to enrich for GIF confirms the existence of an antibody cross-reactivity. In addition, the recombinant GIF produced in eukaryotic cells is not purified to homogeneity. It is an enriched preparation from cells that likely produce MIF on their own, and no experiment employing negative controls are shown.

5. Furthermore, there is no disclosure in the '168 patent or in the published literature shown that the anti-GIF mAbs are actually specific for MIF. All blots shown are carried out using enriched preparations of GIF. No blots against complex protein preparations (e.g., of serum, cell or tissue extracts) are ever shown. The spectrum of proteins that the anti-GIF antibodies can bind to is therefore not known, and in fact that GIF and MIF are actually different proteins.

In relying upon the theory of inherency, the Office Action "must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Further, the Federal Circuit held that "[I]nherency..., may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) and MPEP §2112.

In the absence of the demonstration of the specificity to MIF, the utility of anti-GIF antibody in a MIF assay is unknown. Particularly, all of the blots shown with the anti-GIF mAb

in the '168 patent are against highly enriched/fractionated GIF preparations. The 12.5 kDa and 14.4 kDa size difference between MIF and GIF, respectively, is ignored. In fact, Ishizaka et al. report that the 14.4 kDa band identified by the monoclonal antibody is likely a degradation product of a 41 kDa molecule (see page 1906 of Katamura et al., 1990). As such, there is no evidence provided that the anti-GIF mAbs disclosed in the '168 patent are specific for MIF. Further considering the fact that Ishizaka et al. specifically disclose that the cloned GIF does not have MIF activity (col. 46, line 47 to col. 47, line 4), it can be concluded that GIF and MIF are different molecules.

In summary, the '168 patent fails to disclose a diagnostic method for determining the amount of MIF in a sample using an anti-MIF antibody which binds specifically to the human MIF protein that has a molecular weight of approximately 12.5 kDa and has MIF biological activity. Accordingly, Ishizaka et al. ('the 168 patent) does not teach each and every element as set forth in the claims of the present invention, and therefore, Ishizaka et al. do not anticipate the present invention.

Thus, the grounds for this rejection have been obviated and withdrawal of the 35 U.S.C. §102 rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112

Claims 66-68, 73-75, 81-82, 85, and 87-89 stand rejected under 35 U.S.C. § 112 as failing to comply with the enablement requirement for the reasons set forth on pages 3-4 of the Outstanding Office Action. Applicants respectfully traverse the rejection.

The Examiner alleges that the present specification does not demonstrate an antibody which can immunologically distinguish between GIF and MIF, and that there are no teachings in the specification as to how one of skill in the art could arise such an antibody. The Examiner's

contention is respectfully traversed. Applicants respectfully submit that independent claims 66, 81 and 85 are directed to methods for detecting MIF protein using an anti-MIF antibody that binds specifically to an MIF protein having a molecular weight of approximately 12.5 kDa and having MIF biological activity. In this regard, the specification describes the production of anti-MIF monoclonal antibodies that specifically recognize a 12.5 kDa protein on Western blot and demonstrate the anti-MIF neutralization activity (p.114, line 19 - p.117, line 14). The specification further discloses the development of quantitative sandwich ELISA for MIF (p.117, line 16 - p.118, line 33). Accordingly, Claims 66, 81 and 85 are fully enabled by the specification.

The Examiner alleges that if one skilled in the art practices applicant's invention using the teachings of the specification it would result in simultaneously detecting GIF and MIF, and therefore would not allow one of skilled in the art to only detect MIF. Applicants respectfully disagree.

It is known to one skilled in the art that MIF and GIF have different post-translational modification patterns which lead to different biological activities. Therefore, an anti-MIF antibody which specifically binds to MIF will not necessarily bind specifically to GIF. Furthermore, Applicants have attached Declaration of Robert A. Mitchell and would like to call the Examiner's attention to the fact that there is no evidence showing the existence of GIF *in vivo*. As such, it is therefore not possible to detect GIF in a naturally derived body sample as GIF has not been demonstrated to exist in such a sample. In this regard, one skilled in the art can practice the present invention without undue experimentation.

Thus, the grounds for this rejection have been obviated and withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

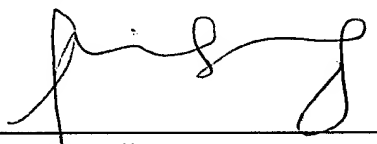
CONCLUSION

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants, therefore, respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact Ping Wang, M.D. (Reg. No. 48,328) at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP



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